REMARKS

Amendments

Claims 7, 13, 19, and 25 are amended above solely to correct the misspelling of "substituent", and not for reasons relating to patentability.

Claims 31-34 are amended to replace "general formula" with – the formula , which Applicants submit does not change the meaning or scope of the claims, and thus is not related to patentability.

Claim 33 is additionally amended add a missing valance to "-NR^5" and "–O", and to remove the unnecessary language "such as a halogen group as defined in the specification." Applicants submit that this language is superfluous, and that its removal neither adds nor subtracts from the claim, and thus is not related to patentability.

Rejection under §112, First Paragraph

A. "Heteroalkyl"

Claims 1-11, 13-17, and 19-36 were rejected under §112, first paragraph, on the assertion that the specification fails to enable R^2 equal to all heteroalkyl rings, and that R" is not enabled for all heteroalkyl rings. Applicants respectfully traverse.

As an initial observation, Applicants note that the claims do not recite "heteroalkyl rings" per se. The definition of R^2 recites "heteroalkyl", which is defined in the specification (see page 5, lines 20-30) as alkyl substituted with 1-3 moieties selected from $-OR^a$, $-NR^bR^c$, and $S(O)_nR^d$, where R^a, R^b, R^c, and R^d may each independently be H, alkyl, cycloalkyl, cycloalkyl-alkyl, etc. Applicants submit that preparation of such moieties is not outside the level of ordinary skill in the art, nor is there introduction into an alkyl radical (e.g., by nucleophilic displacement of a halogen), nor is the introduction of the heteroalkyl radical into the ring structure (e.g., by electrophilic substitution). The specification at page 18, line 2, cites J. DeRuiter et al., J Med Chem (1986) 29:2024-28 as a reference showing synthesis of substituted quinolinones that can be useful as starting materials for preparation of compounds of the invention. See also Browner et al., US 2002-0161004, which describes the preparation of a number of compounds that can be used as intermediates in the synthesis of compounds of the present invention. Browner in turn cites a number of

references that describe the synthesis of substituted isatins, from which suitable starting materials can be made. See, e.g., P.G. Gassman et al., J Org Chem (1977) 42(8):1344-48; F. Ozawa et al., J Org Chem (1986) 51:415-17; P. Hewawasam and N.A. Meanwell, Tet Lett (1994) 35(40):7303-06; and E.A. Kraynack et al., Tet Lett (1998) 39:7679-82. Copies of these references will be sent separately by mail.

In the same manner, the claims do not recite "heteroalkyl rings" with respect to R", but recite "heteroalkyl", which is defined as described above. As R" is attached to a simple phenyl ring, the chemistry is even more straightforward, and is within the level of ordinary skill in the art.

Thus, Applicants submit that synthesis of the compounds is fully enabled.

The specification enables the use of the claimed compounds beginning at page 26, line 10, including a description of administration and formulation beginning at page 27, line 19. All compounds of the invention may be administered by the methods taught in the specification, regardless of the choice of moieties for R^2 and R". MPEP §2164.01(c) provides in relevant part:

> "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. [Cites omitted.]"

The Examiner's concern appears to be more in the nature of ***utility*** for compounds in which R^2 is other than H, or R" is other than halo or alkoxy. However, Applicants have demonstrated utility for compounds that are closely related structurally (e.g., where R^2 is H and R" is halo or alkoxy), and thus one may reasonably infer that the related compounds are also useful to some degree. See, e.g., MPEP §2107.03(II): "Courts have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility as being supportive of an assertion of therapeutic utility for a new compound." The MPEP further cites In re Gardner (CCPA 1973) 475 F.2d 1389, 177 USPQ 396, "in which the court held that utility for a genus was found to be supported through ***a showing of utility for one species***." (emphasis added)

In the present case, Applicants have demonstrated utility for a number of compounds (see Specification, page 45, table at lines 3-5). Since these compounds are shown to have activity, they support a finding of utility for structurally related compounds, e.g., the compounds in which R^2 is other than H, and/or R" is other than halo or alkoxy.

Thus, Applicants respectfully submit that the claims are fully enabled, and that the claimed invention is useful, within the requirements of §112 and §101.

B. "Treatment"

Claim 28 was rejected under §112, first paragraph, on the assertion that the specification fails to enable "the method of treating all diseases related claimed, many of which are unrelated." Applicants respectfully traverse.

Claim 28 recites the treatment of inflammatory diseases selected from myositis, synovitis, arthritis (rheumatoid arthritis and osteoarthritis), gout, back pain, dental pain, sports injuries, sprains, strains, headache, tendonitis, ankylosing spondylitis, and bursitis. These diseases are all examples of inflammation and/or pain, and share common mechanisms of action that may be inhibited by a compound of the invention. Standard modes of administration exist, and may be used in the method of the invention. Treatment of these diseases is supported in the specification at, inter alia, page 27, lines 11-23, in addition to the description of formulation and administration provided at page 27, line 20 to page 29 line 9. Examples 9-12 describe inhibition of COX I and COX II, anti-inflammatory activity, eicosanoid synthesis inhibition, and analgesic activity of compounds of the invention, respectively. These include in vivo assays long-recognized as relevant predictors of anti-inflammatory activity and analgesic activity, and thus are relevant to the treatment of pain and inflammation claimed. Thus, Applicants submit that treatment of the claimed diseases are in fact enabled in the specification.

As noted above, "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." (MPEP §2164.01(c)). The section further states:

> "For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph."
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> "If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, **if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.**" (MPEP §2164.01(c), emphasis added.)

In the present case, the compounds of the invention can be administered by standard methods, e.g., orally, systemically, etc. Accordingly, Applicants submit that the rejection is thus overcome.

Rejection under §112, Second Paragraph

A. "Inflammatory disease, cancer, or pain"

Claim 27 was rejected as indefinite under §112, second paragraph, on the assertion that the phrase "inflammatory disease, cancer, or pain" is indefinite. Applicants respectfully traverse.

"Inflammatory disease" refers to a disease characterized by inflammation, and thus identifies a plurality of diseases by the mechanism that is common to all of them. As the compounds of the invention inhibit COX enzymes, and thus inhibit the production of an inflammatory response, it is not surprising that the compounds treat all such inflammatory diseases, and no further limitation is necessary. Similarly, the same inflammatory pathway that includes COX also results in the generation of pain: thus, the fact that the compounds of the invention are capable of ameliorating pain from any of a variety of causes is not surprising, and no further limitation is required.

The compounds of the invention are also believed to be effective against cancer in general. Applicants note that several COX-II specific drugs have shown activity against a wide variety of cancers. As noted recently by scientists at the US National Cancer Institute (W.F. Anderson et al., Cur Pharma Design (2002) 8(12):1035):

> "Nine studies of COX-2 selective inhibitors - two involving NS-398, one with MF tricyclic, two with nimesulide, one with rofecoxib, and three with celecoxib – have proven the efficacy of this subclass of agents in reducing aberrant crypt foci (ACF) and CRCs in carcinogen- and genetically-induced rodent models [cites omitted]. In addition, profound preventive effects have been reported with COX-2 selective inhibitors in animal models of breast [cites omitted], skin [cites omitted], bladder [cites omitted], lung [cite omitted], and prostate [cite omitted] cancer."
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> "Based on these impressive safety and preclinical efficacy data, COX-2 selective inhibitors have advanced into clinical chemoprevention trials." Anderson et al. at p. 1052

See also: X-Z Ding et al., Pancreatology (2001) 1:291-99 (pancreatic cancer); G. Singh-Ranger, J Clin Pharmacy Therap (2002) 27:321-27 ("A wealth of experimental data now exist to support the hypothesis that COX-2 is involved in the pathogenesis of breast cancer."); E. Rahme et

al., Gastroenterol (2003) 125:404-12 (colorectal cancer and adenomas); J.A. Sánchez-Alcázar et al., Lung Cancer (2003) 40:33-44 (non-small cell lung cancer); and V.E. Steele et al. [again, the US NCI], Mutation Res (2003)523-524:137-44 ("Besides FPA [familial adenomatous polyposis], celecoxib is being studied for prevention of hereditary non-polyposis colorectal cancer, sporadic colorectal adenomas, bladder cancer, actinic keratosis, and Barrett's esophagus...." P. 141). Copies of these references will be sent separately by mail. Thus, Applicants submit that, given the diversity of cancers that are believed to be treatable with COX-2 inhibitors, it is not surprising that the compounds of the invention are effective against a wide variety of cancers, and thus no further limitation is required.

B. "General Formula"

Applicants submit that the rejection of claims 31-34 as indefinite for use of the phrase "general formula" is overcome by the above amendments of the rejected claims.

C. "Such as a halogen..."

Claim 33 was rejected as indefinite for recitation of the phrase "such as a halogen group as defined in the specification." Applicants submit that the rejection is overcome by the above amendment of claim 33, removing the unnecessary language.

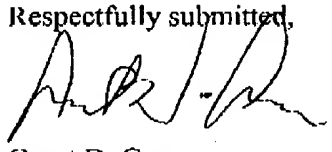
D. "Optional oxidation"

Claim 33 was rejected as indefinite for use of the phrase "optional oxidation." Applicants respectfully traverse. Oxidation is optional in this method because the $-S(O)_{0-2}R^{12}$ substituent need not be oxidized: the optional oxidation is employed to convert $-SR^{12}$ to $-S(O)R^{12}$ or $-S(O)_2R^{12}$.

CONCLUSION

In light of the foregoing, Applicants respectfully submit that all rejections of the pending claims have thus been overcome, and that the application has been put into condition for allowance. Applicants hereby request a Notice of Allowance for the same.

Respectfully submitted,



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